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EXAMINER	
REDDIG, PETER J	

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1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/530,488	TJOTTA, ENOK	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 17 December 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because

(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☒ They raise the issue of new matter (see NOTE below);

(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: See *Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
The status of the claim(s) is (or will be) as follows:
Claim(s) allowed: _____.
Claim(s) objected to: _____.
Claim(s) rejected: *28-41,44,46 and 61*.
Claim(s) withdrawn from consideration: *42,43,45 and 47-60*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/Karen A Canella/
Primary Examiner, Art Unit 1643

Continuation of 3. NOTE: Applicant argues that amendment contains no new matter and entry of this amendment under 37 CFR §1.116 is respectfully requested because it cancels claims, complies with a matter of form set forth in the Office Action, and places the application in condition for allowance.
Applicant argues that the Office Action of September 17, 2008 (to which this paper responds) was the first action on the merits in which claims were rejected for statutory reasons. As a result, there has been no opportunity for a clear issue to develop between the applicant and the Office. See MPEP 706.07(b) for the criteria for a holding of finality on the first action.
Applicant's arguments have been considered, but have not been found persuasive because the method comprising the combination of steps in claim 28 raises the issue of new matter, see response to written description/new matter rejection below. Additionally, it is noted that the non-final rejection of September 11, 2007 was based on statutory rejections and the new rejections in the final rejection were based on Applicant's amendments. Thus, Applicant's arguments with regard to holding finality on the first action are not found persuasive because the final rejction of September 17, 2008 was the second action on the merits .

Continuation of 11. does NOT place the application in condition for allowance because: Claims 28-41, 44, 46, and 61 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth in the Office Action of September 17, 2008, section 6, pages 4-6.
Applicant argues that The Office Action asserts that the claims omit essential steps such as the steps for conducting an in vitro clonal test, the steps for testing the effect that different degrees of local collocation of cells has on the effect of the agent, and the steps for an in vivo test of clonal growth of immune cells. The comments in the Office Action have been considered, and these steps are now set forth in detail in independent claim 28. Applicant's argue that the Office Action also points out issues of antecedent basis. The amended claim set has full antecedent basis.

Applicant's arguments have been carefully considered, but have not been found persuasive because the amendment has not been entered and will not be entered for the reasons set forth above, therefore the claims have not been amended and the rejections remain for the reasons previously set forth .

Applicant argues that the Office Action further asserts that the terms "liberation of the ceils" and "potential toxin" as being indefinite since the specification does not teach what the terms encompass. The liberation of the cells is when cells are liberated from the tumour and will initiate local infiltration or a metastasizing process elsewhere in the body. This has been described in several experiments (experiments 4,9,14,18,23,25 and 26) in the specification and this term is a common expression for this process and obvious for one skilled in the art.

Applicant argues that potential toxins is a common expression to a toxin which are not toxic in healthy peoples, but unusual high concentrations, a special constitution, metabolism or disease may make intake of such potential toxins toxic. Intake of such compounds may occur through food, health food, drugs, air, water, cosmetics, and pollutions or by direct contact.

Applicant's argument have been considered, but have not been found persuasive. With regard to liberation of cells, the claims are not limited to the cells being liberated from a tumor, thus Applicant is arguing limitations not found in the claims and in the absence of clear description of liberation of cells in the specification, the term "liberation of cells" is indefinite. With regard to potential toxins, Applicant argues that non-toxic substances may become toxic at some undefined concentration or other special situation. It is noted that Section 2173.05(b) of the MPEP states that a claim may be rendered indefinite by reference to an object that is variable. In the instant case a potential toxin is variable because a compound may or may not be a toxin under certain, undefined conditions. Given the variable nature of a potential toxin and the undefined nature of when a compound becomes a toxin, the metes and bounds of what is encompassed by a potential toxin are indefinite.

Claims 28-41, 44, and 46 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons set forth in the Office Action of September 17, 2008, section 7, pages 6-7.

Applicant argues that the Office Action asserts that the method for testing and selecting an agent to determine whether the agent inhibits of stimulates clonal growth comprising steps a) through d) are not supported in the specification as filed. This issue was addressed in the Amendment filed January 22, 2008.

Applicant argues tha however, the remarks filed January 22, 2008 were found not to be persuasive, and the Office Action asserts that since the specification did not support the method comprising the combination of the steps in claim 28, including step d).
Applicant argues that first, step d) has been amended to be simplified to remove the term 'of the subject."

Applicant's arguments have been carefully considered, but have not been found persuasive because the amendment has not been entered and will not be entered for the reasons set forth above, thereforethe claims have not been amended and the rejections remain for the reasons previously set forth .

Applicant argues that also, an objective standard for determining compliance with the written description requirement is: "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d iiii, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Ear-Mar-Co.,

Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting IN re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)}.

Applicant argues that the claimed method is a three phase test (page 4, lines 23 - 25, page 42 line 9 and page 38 - 42 line 22), comprising a clonal test (page 38) followed by collocation inhibition test (page 40) and finally a test for influencing the development of metastasis (page 41) where the assay detecting the effect on clonal inhibition performed either in cell culture, in mice or in another animal is included. This disclosure reasonably conveys that the inventor has possession of the invention when the application was filed.

Applicant's arguments have been considered, but have not been found persuasive because, as specifically argued by the Applicant, the specification is drawn to a three phase test not a four phase/step test as claimed. Thus, Applicant had not conveyed with reasonable clarity as of the filing date sought the four phase/step test as claimed and the rejection is maintained.

Applicant argues that further, possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it),

Applicant argues that in this case, the specification has extensive experimental results demonstrating possession of the invention, as is evidenced, e.g., by the 65 pages of drawing figures. Applicant argues that as a result, the present invention is fully supported by the specification as filed.

Applicant's arguments have been considered, but have not been found persuasive because the drawings and experimental results, although showing individual test, do not describe or show possession of the four step test as claimed in claim 28 and its dependent claims.

Claims 28-32, 34-36, 38-41, 44, 46 and 61 remain rejected under 35 U.S.C. 102(b) as being anticipated by Prechel et al. (Cancer Letters, 1995, 92: 235:242) as evidenced by Car et al. (Toxicologic Pathology, 1999, Vol. 24:58-63) for the reasons set forth in the Office Action of September 17, 2008, section 8, pages 8-12.

Applicant argues that PRECHEL et al. evaluated the effects of IL-12 on immune parameters and tumor progression in an animal tumor model in which tumor production of GM-CSF leads to myelopoietic stimulation giving rise to an increased number of immune suppressive GM- progenitor Gells that suppress anti-tumor responses. IL-12 augmented the myelopoietic stimulation that is induced by the progressively growing tumor, although it diminished the proliferative potential of the myeloid progenitor cells. The presence of GM-CSF-induced immune suppressor cells in the bone marrow, spleen and tumor was not reduced by IL-12. T cell functions in tumor bearers were suppressed and this generally was not overcome by IL-12 treatment. While IL-I2 enhanced tumor-specific cytolytic activity in the draining lymph nodes, there were no effects on the frequency of intratumoral CD8+ T-cells, on the growth of s.c. tumors, or on the formation of metastases.

Applicant argues that In PRECHEL et al., there is no effect of IL-12 on metastases, and the article does not describe a specific affection of clonal growth that is different for collocated and scattered identical cells.

Applicant argues that in contrast, the immune modulating effect of the specific clonal inhibitors of the present invention is a side- effect that is not wanted in connection with treatment of tumors or viral infections and is probably significant only for primary immune reactions. The effect on virus production is also linked to the specific nature of the inhibition of clonal growth since the metabolism of collocated identical cells is not significantly affected. Only marginal effects may be present.
Applicant argues that therefore, PRECHEL et al. fail to consider specific clonal inhibitors or enhancers, and IL-12 has no effect on formation of metastases. Applicant argues that therefore, this PRECHEL e tal. includes no relevant counter-arguments against my patent application.

Applicant's arguments have been considered, but have not been found persuasive because Applicant is arguing outcomes (affection of clonal growth that is different for collocated and scattered identical cells) of the testing method which are not claimed and do not affect the structure of the steps of the claimed methods of testing of agents for affects on clonal growth. The claims encompass testing and selecting any agent wheter or not it has a positive or negative result in the clonal test. Thus, Preschel et al. anticipates the claimed methods.

Applicant argues that the Office Action refers to CAR et al. as evidence of IL-12 is a heterodimeric cytokine produced by several types of cells but also has toxic effects.
Applicant argues that however, CAR et al. conclude that recombinant murine interleukin (IL) 12 (rmIL-12) exhibits antitumor, antiviral, and antimicrobial activities and can modify allergic inflammatory reactions in animals models. Recombinant human IL-12 (rhIL-12) is currently in clinical trials for treatment of cancer, asthma, and viral hepatitis.

Applicant argues that the specific clonal inhibitors, however, do not have general anti-tumor, antiviral, antimicrobial activities. Treatment with specific clonal inhibitors is expected only to inhibit activity in identical cells that were sparsely seeded in cultures or sparsely distributed among other cells in the body. The article does not describe an activity of IL-12 and related substances that are confined to only scarcely distributed identical cells in cultures or animals.
Applicant argues thattherefore, the conclusion must be the same for both PRECHEL et al. and CAR et al.

Applicant argues that PRECHEL et al. thus fail to consider specific clonal inhibitors or enhancers and thus fails to anticipate a claimed embodiment of the present invention.

Applicant's arguments have been considered, but have not been found persuasive because Applicant is arguing limitations, i.e. using clonal inhibitors or enhancers in the claimed methods, that are not found in the claims. The agents used in the claimed method are not limited to being clonal inhibitors or enhancers, thus the use of IL-12 anticipates the claimed method.

Claim 33 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Prechel et al. (Cancer Letters, 1995, 92: 235:242), in view of De Asua et al. (Proc. Natl. Acad. Sci USA, 1973, 70:1388-13920) and in view of Kamei H. (Cell Biol. Int. Rep. Jan. 1987, 11 (1): 35-41).

Applicant argues that the Official Action acknowledged that PRECHEL et al. fail to teach using BHK21/c13 and BHK21/C13 cells transformed with polyoma virus. The Official Action turns to DE ASUA and KAHEI.

Applicant argues that the DE ASUA et al. reference shows that BHK 21/13 fibroblasts grown in the presence of insulin show some characteristics of a transiormed strain. The effect is shown both in agar and when grown on surface.

Applicant argues that in the experiments described in the present invention, insulin induces growth of normal cells in soft agar medium. Then specific clonal inhibitors can inhibit these cells, but only when they were sparsely distributed in the culture. This is possible since insulin stimulates both collocated cells and sparsely seeded cells in culture.
Applicants argue that therefore, the conclusion must be the same as for PRECHEL et al. and CAR et al., and DE ASUA et al. fail to consider specific clonal inhibitors or enhancers and is not a relevant counter-argument against my patent application.

Applicant's arguments have been considered, but have not been found persuasive because Applicant is arguing limitations, i.e. using clonal inhibitors or enhancers in the claimed methods, that are not found in the claims. The agents used in the claimed method are not limited to being clonal inhibitors or enhancers, thus Applicant arguments are not found persuasive.

Applicants argue that KAMEI focuses on a test that may show inhibition of anchorage independent growth of transformed cells that may be suppressed by chemicals as retinoic acid. Anchorage independent growth is a growth pattern that transformed cells may show when growing on a surface, also called criss-cross appearance.

Applicant argues that there is a connection between this appearance and the ability that such transformed cell lines have when growing in soft agar: they can form colonies in an agar where the untransformed parent cell line is unable to form colonies.

Applicant argues that therefore, what this test does is performed to select compounds with the ability to revert temporarily or may be more permanently, the transformed phenotype.

Applicant argues that moreover, not all fetal bovine sera (FBS) supported the suppression of anchorage independent growth of retinoic acid, and insulin enhanced the anchorage independent growth in both types of sera even in the presence of retinoic acid.
Hiroia Kamei's article may have been a logical counter argument against the present invention if the content of claim 28 was only: "A method for testing and selecting an agent to determine whether said agent inhibits or stimulates clonal growth."

Applicant's arguments have been considered, but have not been found persuasive because applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Thus, for the reasons previously set forth it would have been prima facie obvious at the time the invention was made to use the BHK21/c13 cell agar colony assay of De Asua or Kamei in combination with the method of Prechel et al. to determine the effect of IL-12 on BHK21/c13 cell anchorage independent growth.

Applicants argue that but there is more: Claim 28, b) "testing the effect those different degrees of local collocation of cells has on the effect of said agent on cloning." This is elaborated in claims 48-52.

Applicants argue that the selection of agents by the test described in the specification is based on the specific inhibition or specific stimulation of clonal growth of cells either seeded sparsely in (agar) culture or transplanted as single cells sufficiently diluted and scattered in tissues. No such inhibition or stimulation of growth of single cells occurs if these cells are locally congregated (collocated) either in culture or in the animal, it is important to be aware that other cells in the animal do not affect the degree of collocation of the transplanted identical cells and thus not the specific inhibition or stimulation of the transplanted cells. It is only the distance between the identical transplanted single cells that counts, not the number of other cells in the body of the animal in the same area.

Applicant argue that therefore, development of local infiltration or metastases as well as growth of clones resistant to ongoing treatment will be inhibited or come to a stop by the specific clonal inhibitors detected and selected by the test.
The conclusion is that Kamei's article does not consider specific clonal inhibitors or enhancers and is not relevant to the present invention.

Applicant's arguments have been considered, but have not been found persuasive because applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Thus, for the reasons previously set forth it would have been prima facie obvious at the time the invention was made to use the

BHK21/c13 cell agar colony assay of De Asua or Kamei in combination with the method of Prechel et al. to determine the effect of IL-12 on BHK21/c13 cell anchorage independent growth. Additionally, Applicant is arguing outcomes (inhibition of local infiltration or metastases as well as growth of clones resistant) of the testing method which are not claimed and do not affect the structure of the steps of the claimed methods of testing of agents for affects on clonal growth. The claims encompass testing and selecting any agent wheter or not it has a positive or negative result in the clonal test.

Claim 37remains rejected under 35 U.S.C. 103(a) as being unpatentable over Prechel et al. (Cancer Letters, 1995, 92: 235:242) in view of US Pat. No. 4,744, 985 (Tami et al., May 17, 1988).

Applicant argues Regarding TAMAI et al., the Abstract sets forth that substances having carcinostatic and immunostimulating activity, which are obtained from a culture or its supernatant fluid prepared by culturing bacteria belonging to the Fusobacterium genus. The substances are useful for the treatment of cancerous diseases in lower warm-blooded animals. This disclosure concerns such substances and a process for preparing the same and a carcinostatic agent containing the same.

Applicant argues that column I, third paragraph of TAMAI et al. states: ".a specific component obtained from the supernatant fluid has a carcinostatic activity in lower warm-blooded animals; that said component has substantially no effect of inhibiting the formation of a colony of cancer cells in a colony forming assay method, and has not a carcinostatic activity by killing the cancer cells."

Applicant argus that is, TAMAI et al. teaches that the formation of colonies is not inhibited by these substances in a colony forming assay. That is completely different from compounds selected by my method described in my patent application where the inhibition is specifically directed against clonal growth of scarcely distributed identical cells.

Applicant argue that table 2 of TAMAI et al. indicates that: all fractions from TF-100 to TF-150 had an immune-stimulating activity.

Applicant argues that in contrast, the selected specific clonal inhibitors of the present invention do not stimulate immunity. The primary immune reaction is, on the other hand, expected to be significantly suppressed. Table 2 indicates that: all fractions from TF-100 to TF-150 inhibited Ehrlich solid tumor. This effect of TF-I00 and TF-120 is not described.

Applicant argue that it is thus noted that the best specific clonal inhibitor 4-OH-OPB stimulated growth of Ehrlich solid tumor. Therefore, these fractions have nothing in common with the inhibitor of the present invention and there is no reason to believe that the specific clonal stimulators detected by my method would inhibit Ehrlich solid tumors.

Applicant argues that the effects of the extracts of Tamai et al. are not thus in accordance with the effects of specific clonal inhibitors or stimulators detected by the method of the present invention. As a result, no combination of the secondary references with PRECHEL et al. is sufficient to alleged prima facie unpatentability. Even if this unpatentabilty could be alleged, it would by dissipated by the unexpected results shown in the Examples and the drawing figures.

Applicant's arguments have been considered, but have not been found persuasive because applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Thus, for the reasons previously set forth It would have been prima facie obvious at the time the invention was made to use the Ehrlich tumor cells of US Pat. No. 4,744, 985 in the examination of tumor growth/metastasis method of Prechel et al. to determine the effect of IL-12 on transplanted Ehrlich tumor cell growth and metastasis. Additionally, Applicant is arguing limitations not found in the claims, specific clonal inhibitors or stimulators, thus these arguments are not found persuasive. Applicant's assertion of unexpected results have not been found persuasive because it is a general allegation with pointing to support for such unexpected results.